Experimental[6]

21-Nor-20-ketocholestane (IIa).—Etioallocholanic acid (5 g.) was converted to the acid chloride by refluxing a benzene solution (30 ml.) with thionyl chloride (25 ml.) for 2 hr. and later evaporating the solvent. A benzene solution of the above (Ia) was run into a stirred solution of diisohexylcadmium, prepared from magnesium (1.88 g.), ether (100 ml.), isohexyl bromide (18.0 g.), and cadmium chloride (8.88 g.), as described by Kurath.[4] The ketone, after chromatography on alumina and recrystallization from acetone, melted at 58–59° (65%), $[\alpha]^{20}D$ +87.3 ± 2.0°.

Anal. Calcd. for $C_{26}H_{44}O$: C, 83.80; H, 11.90. Found: C, 83.92; H, 12.08.

Δ^{20}-Cholestene (20-Dehydrocholestane) (IIIa).—To a solution of butyllithium (80 ml. approx. 1 *N* in ether) in ether, (200 ml.) was added methytriphenylphosphonium bromide (9.5 g.) in lots under nitrogen atmosphere, with efficient stirring. After the addition (1.5 hr.), the orange-yellow solution was stirred for 6 hr. A solution of 21-nor-20-ketocholestane (IIa) (2.5 g.) in ether (100 ml.) was run slowly into the reaction vessel (1 hr.), and the mixture was stirred for an additional 4 hr. and allowed to stand overnight at room temperature. Ether was replaced by tetrahydrofuran, the mixture was refluxed and worked up as described by Sondheimer,[1] and the oily material was chromatographed on alumina. Elution with petroleum ether gave (IIIa) (1.8 g.) melting at 58–60°, $[\alpha]^{20}D$ +11.4 ± 2.0°.

Anal. Calcd. for $C_{27}H_{46}$: C, 87.49; H, 12.51. Found: C, 87.66; H, 12.57.

Hydrogenation of 20-Dehydrocholestane.—20-Dehydrocholestane (IIIa) (500 mg.) was dissolved in ethanol (100 ml.) and hydrogenated over 5% palladium–calcium carbonate (100 mg.) catalyst. When the absorption of hydrogen had stopped, the catalyst was filtered and evaporated. After repeated chromatography and crystallization from acetone, a product melting at 79–80° was obtained (70 mg.), which showed no depression on admixture with an authentic sample of cholestane. The mother liquors after evaporation gave an intractable mixture melting above 40°.

21-Nor-20-ketocholestan-3β-ol Acetate (IIb).—3β-Acetoxyetioallocholanic acid (4 g.) was converted to the acid chloride (benzene 30 ml. and thionyl chloride 25 ml.) and a benzene solution of the acid chloride (Ib) was run into diisohexylcadmium [prepared from magnesium (1.5 g.), isohexyl bromide (14.3 g.), and cadmium chloride (7.0 g.) as described before]. The ketone was acetylated in the usual way and crystallized from methanol, m.p. 88–89° (3.6 g.), $[\alpha]^{20}D$ +70.8 ± 3.0°.

Anal. Calcd. for $C_{28}H_{46}O_3$: C, 78.09; H, 10.77. Found: C, 78.27; H, 10.84.

Δ^{20}-Cholesten-3β-ol Acetate (IIIb).—21-Nor-20-ketocholestan-3β-ol acetate (IIb) (900 mg.) was converted to the 20-dehydro compound (IIIb) by treatment with butyl lithium and methyltriphenylphosphonium bromide as above. The reaction product was acetylated (pyridine acetic anhydride at room temperature) and, after chromatography and crystallization from methanol, was obtained as platelets, m.p. 111–112°, $[\alpha]^{20}D$ +1.2 ± 1.2°.

Anal. Calcd. for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 81.35; H, 10.98.

Cholestan-3β-ol, 20-Iso, and 20-*N* (IVb, 20-iso and 20-*n*).—Δ^{20}-Cholesten-3β-ol acetate (380 mg.) was dissolved in ethanol (50 ml.) and hydrogenated over palladium–calcium carbonate (100 mg.) as before. Separated from the catalyst, the residue after evaporation was found to be a mixture, and all attempts to separate it into pure components failed.

A similar hydrogenation carried out in glacial acetic acid and platinum oxide gave identical results.

Cholestan-3β-ol acetate (IVa, 20-iso and 20-*n*) (520 mg.) was hydrolyzed in methanolic caustic potash (potassium hydroxide 2 g., water, 5 ml., and methanol, 80 ml.) at refluxing temperature for 4 hr. The hydrolyzed product (465 mg.) was chromatographed on alumina grade II. Elution with benzene–ether (3:7) and (1:9) gave a product (325 mg.) which after recrystallization from ethanol melted at 154–157°. After repeated recrystallizations from ethanol the melting point was sharp at 160–161°, $[\alpha]^{20}D$ 6.0 ± 1.0°.

Anal. Calcd. for $C_{27}H_{48}O$: C, 83.43; H, 12.45. Found: C, 83.58; H, 12.27.

The melting point was depressed on admixture with an authentic sample of cholestanol. Further elution of the column with ether gave a product, m.p. 135–137°, which, after several crystallizations, melted at 143–144° and was identical with cholestanol (mixed m.p. and infrared).

20-Iso-17-*n*-cholestane (IVd).—20-Isocholestan-3β-ol (158 mg.) was dissolved in acetone (60 ml.) and oxidized with 8 *N* chromic acid at 0°. The solution then was diluted and filtered. The precipitate was dried and chromatographed on fluorisil (100 mesh). Elution with benzene–petroleum ether (3:1) gave the ketone (IVc) (123 mg.). Infrared showed band at 1,718 cm.$^{-1}$. This then was converted to the thioketal in the usual manner (ethanedithiol and boron trifluoride). After chromatography and crystallization from acetone, the compound melted at 141–143°.

20-Isocholestan-3-one thioketal (75 mg.) dissolved in dioxane (15 ml.) was refluxed with Raney nickel (3 g.) for 5 hr. The reaction was cooled and filtered; the filtrate was evaporated and crystallized from acetone giving (IVd), m.p. 62–65° (54 mg.). A highly purified analytical sample melted at 67–69°, $[\alpha]^{20}D$ +7.6 ± 0.5°.

Anal. Calcd. for $C_{27}H_{48}$: C, 87.02; H, 12.98. Found: C, 87.10; H, 12.70.

(6) Melting points are uncorrected. Rotations were determined at 20° in chloroform solution. The chromatograms were made with Woelm aluminum oxide, neutral, activity grade I unless otherwise mentioned. Analyses and rotations were performed by the Analytical Services, NIAMD, under the direction of Mr. H. G. McCann.

Synthesis of 3-Trifluoromethyltyrosine[1]

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In a recent paper[2] we reported the synthesis of 2-trifluoromethyl-*dl*-tyrosine and 3-trifluoromethyl-4-methoxy-*dl*-phenylalanine. Attempts to prepare 3-trifluoromethyl-*dl*-tyrosine (I) were unsuccessful, however, because of the hydrolytic instability of the trifluoromethyl group *ortho* to the hydroxyl group.[3]

It has been previously shown[2,4,5] that the Meerwein arylation reaction provides a useful and often, a preferred, route to aromatic α-amino acids. For the synthesis of compound I, it was therefore desirable to prepare the previously unreported key intermediate, 2-trifluoromethyl-4-nitrophenol (II).

(1) Paper No. III in the series on fluorinated aromatic amio acids.
(2) R. Filler and H. Novar, *J. Org. Chem.*, **26**, 2707 (1961).
(3) R. Filler and H. Novar, *Chem. Ind.* (London), 1273 (1960).
(4) R. Filler and H. Novar, *ibid.*, 468 (1960).
(5) R. Filler, L. Gorelic, and B. Taqui Khan, *Proc. Chem. Soc.*, 117 (1962).

Our earlier attempts[2] to prepare this compound from 2-methoxy-5-nitrobenzotrifluoride (III) or the 2-chloro analog, under strongly acidic or basic conditions, invariably led to hydrolysis of the CF_3 group with formation of 5-nitrosalicylic acid (IV).

We have now found that the ether linkage is smoothly cleaved *without* hydrolysis of the CF_3 group when compound III is heated at 210° for twenty minutes with *fused* pyridine hydrochloride. In this way, compound II was readily prepared in 75% yield. If the reaction time was increased or the temperature raised above 210°, the desired product was accompained by increasing amounts of IV. In contrast to these selective conditions, the attempted demethylation of III with hydrobromic acid–acetic acid under long reflux always led to the formation of compound IV as the exclusive product.

The structure of compound II was established by analytical and spectral evidence and by hydrolysis to IV with concentrated sulfuric acid. II was reduced to 2-trifluoromethyl-4-aminophenol (V) in 98% yield in the presence of palladium–charcoal. Compound V was diazotized and treated with acrylic acid[6] in aqueous acetone in the presence of cuprous chloride to give the α-chloro acid, VI, in 71% yield. Ammonolysis of VI with liquid ammonia in a sealed glass tube provided compound I in 79% crude yield. The conversion of III to I was thus accomplished in 41% over-all yield.

The amino acid gave positive ninhydrin and Millon's tests and exhibited typical infrared absorption including the phenolic —OH band. The ultraviolet spectrum was similar to that observed with the 2-trifluoromethyl isomer.[2] The free phenol exhibited maxima at 227 mμ (ϵ 8160) and 285 mμ (ϵ 1840). A bathochromic and hyperchromic shift to 248 mμ (ϵ 12,750) and 308 mμ (ϵ 2990) occurred at pH 11.1, due to generation of the phenolate ion. The marked increase in water solubility of this amino acid and also of the 2-trifluoromethyl isomer, relative to *dl*-tyrosine, may be a result of intermolecular O—H...F bonding in these compounds or of an increase in acidity of the phenolic —OH group.

Two other approaches to compound II merit comment: (1) Ammonolysis of 2-chloro-5-nitrobenzotrifluoride[2] gave 2-amino-5-nitrobenzotrifluoride (VII). The fact that no 3-amino isomer was isolated argues against the elimination–addition ("benzyne") mechanism[7] and in favor of a bimolecular nucleophilic displacement.

The weakly basic amino group in VII was not diazotized in aqueous acid solution.

(2) *o*-Hydroxybenzotrifluoride was treated with nitric acid–acetic acid in the cold to give the new compound, 2-hydroxy-3-nitrobenzotrifluoride, the structure of which was confirmed by acid hydrolysis to 3-nitrosalicylic acid. The presence of compound II could not be detected.

Experimental[8]

2-Trifluoromethyl-4-nitrophenol (II).—To 25 g. of freshly fused pyridine hydrochloride was added 5 g. of 2-methoxy-5-nitrobenzotrifluoride[2] and the mixture heated at 210° for 20 min. The flask was cooled; the reaction mixture was dissolved in ether and diluted with water. After three extractions with ether, the combined extracts were washed with dilute sodium chloride solution and dried over anhydrous sodium sulfate. The solution was evaporated almost to dryness and the residue crystallized from a benzene–petroleum ether mixture to give 3.5 g. (75%) of desired product, m.p. 134–135°.

Anal. Calcd. for $C_7H_4F_3NO_3$: C, 40.57; H, 1.95. Found: C, 40.56; H, 2.01.

Infrared: 3400–3220 cm.$^{-1}$ (vs, broad), —OH stretching; 1170–1050 cm.$^{-1}$ (s), C—F stretching.

When this compound was heated with concentrated sulfuric acid, 5-nitrosalicylic acid, m.p. 234–236°, was obtained. Mixture melting point with an authentic sample showed no depression.

2-Trifluoromethyl-4-aminophenol (V).—II (11.0 g.), dissolved in 150 ml. of 95% ethanol, was reduced by hydrogen in the presence of 300 mg. of 5% palladium on charcoal. After removal of catalyst, the solvent was evaporated to half its original volume and the product which separated was crystallized from ethanol to give 9.22 g. (98%) of product, m.p. 203–204° dec.

Anal. Calcd. for $C_7H_6F_3NO$: C, 47.44; H, 3.42. Found: C, 47.72; H, 3.61.

Meerwein Arylation Reaction with V.—In a flask equipped for magnetic stirring were placed 8.8 g. (0.05 mole) of V and 15 ml. of concentrated hydrochloric acid. Seventy five milliliters of acetone was added, the contents cooled to 0° and 3.45 g. of sodium nitrite in 10 ml. of water added with stirring while the temperature was maintained below 5°. Acrylic acid (0.7 mole) was introduced, the system swept with dry nitrogen for 15 min., 500 mg. of cuprous chloride was added and the mixture stirred for 2 hr. at 20–25°. After dilution with 600 ml. of water, the mixture was extracted three times with benzene and the extracts washed twice with water and extracted four times with sodium bicarbonate. The combined alkaline extracts were acidified with dilute hydrochloric acid, extracted with benzene, washed with water, dried over sodium sulfate, and the benzene solution evaporated almost to dryness to give, after crystallization from benzene–petroleum ether, 9.5 g. (70.9%) of chloro acid, VI, m.p. 129–130°.

Anal. Calcd. for $C_{10}H_8ClF_3O_3$: C, 44.69, H, 3.00, Found: C, 44.39, H, 3.20.

3-Trifluoromethyl-*dl*-tyrosine (I).—A solution of 2.0 g. of α-chloro acid in 10 ml. of ethanol was placed in a Pyrex tube sealed at one end. The tube was cooled in a Dry Ice–acetone bath, and about 50 ml. of liquid ammonia was introduced. The tube was sealed and its contents shaken for 3.5 days at room temperature. The tube was cooled, the seal broken, and the solution transferred to a flask. After excess ammonia had evaporated, the solution was diluted with ether until a faint turbidity developed and then

(6) Although acrylonitrile or acrylic esters generally afford better yields of addition products (ref. 5), the conditions of the subsequent acid hydrolysis of —CN or —COOR to —COOH (ref. 5) was considered detrimental to the stability of the CF_3 group.

(7) The conversion of *o*-chlorobenzotrifluoride to *m*-aminobenzotrifluoride with sodium amide in liquid ammonia has been postulated to proceed *via* a "benzyne" intermediate. J. D. Roberts, C. W. Vaughan, L. A. Carlsmith, and D. A. Semenow, *J. Am. Chem. Soc.*, **78**, 611 (1956).

(8) Melting points were determined on a Fisher-Johns block and are uncorrected.

left for 2 days at room temperature. The semicrystalline solid was warmed at 40–50°, the solid filtered and pressed between filter papers, washed with an ethanol–ether mixture, and dried. Crystallization by dissolving in ethanol and precipitating with ether gave 1.26 g. (79%) of slightly impure material. Further crystallizations gave purer material, m.p. 212–219° dec. The water-soluble acid gave postive ninhydrin and Millon's tests.

Anal. Calcd. for $C_{10}H_{10}F_3NO_3$: C, 48.19; H, 4.04; N, 5.62. Found: C, 48.10; H, 4.16; N, 5.49.

Infrared: 3600–3400 cm.$^{-1}$ (m, broad), —OH stretching; near 3100 cm.$^{-1}$ (s), —NH_3^+ stretching, part of broad band in 3200–2900-cm.$^{-1}$ region, including C—H stretching; twin bands at 1650 cm.$^{-1}$ (N) and 1615 cm.$^{-1}$ (vs), —COO^- stretching.

Ultraviolet spectra were measured in 95% ethanol (see discussion).

2-Amino-5-nitrobenzotrifluoride (VII).[2]—This compound was prepared in 97% yield by heating 2-chloro-5-nitrobenzotrifluoride with ammonia in a stainless steel bomb at 90° for 18 hr.

VII was heated with concentrated sulfuric acid to give yellow needles, m.p. *ca.* 270°, presumably 5-nitroanthranilic acid.[9] This material was treated with hot concentrated potassium hydroxide and the resulting solution acidified to give 5-nitrosalicylic acid, m.p. 234–235°. There was no depression on admixture with an authentic sample. VII gave the latter compound directly on reaction with alkali.

Attempted Synthesis of II from VII.—VII was treated with dilute sulfuric acid and potassium nitrite at 0° and the resulting solution slowly added to a boiling, saturated solution of copper sulfate under steam distillation conditions. The distillate was extracted with ether, the ethereal solution dried, and then evaporated to yield a brown oil. The oil was crystallized several times from ethanol–water mixtures to give a product melting at 95°, shown to be identical with starting material.

Nitration of *o*-Hydroxybenzotrifluoride.[10]—A. *o*-Hydroxybenzotrifluoride (5.0 g.) was placed in a 250-ml. Erlenmeyer flask and a solution containing 15 ml. of glacial acetic acid, 7.5 ml. of nitric acid, and 7.5 ml. water, was added while the flask was swirled in an ice bath. After the solid had dissolved, the flask was placed in the ice box overnight. No solid formed during this period, but a few small crystals adhered to the aluminum foil which covered the stopper. Several pieces of aluminum foil were added while the contents were swirled and the temperature allowed to rise. The contents of the flask darkened and after cooling overnight, there was obtained 2.6 g. of yellow crystals, m.p. 68–70°. Crystallization from an ethanol–water mixture yielded a product, m.p. 71.2–72.0° (cor.).

Anal. Calcd. for $C_7H_4F_3NO_3$; C, 40.59; H, 1.95; mol. wt., 207. Found: C, 40.25; H, 2.15; mol. wt., 216 (Rast).

Hydrolysis of this material with concentrated sulfuric acid gave a product, m.p. 146–148°, after crystallization from ethanol–water. Mixture melting point with authentic 3-nitrosalicylic acid showed no depression. The original product was, therefore, 2-hydroxy-3-nitrobenzotrifluoride.

B. VIII reacted with 8 *N* sulfuric acid and potassium nitrite to give, after work-up, yellow crystals of 2-hydroxy-3-nitrobenzotrifluoride, m.p. 69–71°.

Analyses were conducted by Micro-Tech Laboratories, Skokie, Ill., and by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

Infrared spectra were measured with a Perkin–Elmer Model 21 double beam spectrophotometer using KBr pellets. Ultraviolet spectra were obtained on a Beckman DK-2 recording spectrophotometer.

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Aliphatic Nitrones

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Attempts to prepare aliphatic nitrones by the condensation of aliphatic aldehydes and N-alkylhydroxylamines, a reaction which yields C,C-disubstituted aliphatic nitrones from aliphatic ketones,[1] results only in the formation of dimers[2] or products from secondary reactions.[3] Alicyclic five-membered ring nitrones have been prepared either by reduction of γ-nitro ketones[4,5] or by oxidation of the corresponding hydroxylamine derivatives.[6] However, the parent six-membered ring nitrone has not been obtained by these methods since 1,3-dipolar addition takes place to form the dimer.[2] Recently we obtained N-methyl-C-4-hydroxytetramethylene nitrone from 5-hydroxypentanal *via* its cyclic N-hydroxylamino acetal.[7] To our knowledge this is the first synthesis of an aliphatic nitrone from the corresponding aldehyde.

Ruppert used hydrogen peroxide to oxidize aliphatic azomethines and obtained aliphatic nitrones,[8] which we have also succeeded in synthesizing by using the same reagent to oxidize O,N-cyclic acetals of 5-hydroxypentanal. These acetals are readily made by treating the cyclic hemiacetal of 5-hydroxypentanal with primary amines in the presence of potassium carbonate[9]; their infrared spectrum showed no absorption in the C=N region.

The N-alkyl-C-4-hydroxytetramethylene nitrones Ia and Ib obtained in this way could be distilled *in vacuo* without decomposition. Their infrared spectra on a sodium chloride plate showed a strong C=N absorption at 6.05 μ and a medium strong band at 6.4 μ which we attribute to the =N → O group, since in a polar solvent (chloroform) it shifted to 6.55 μ.[5]

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